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Chapter 4

A Matter of Taste: Capsaicinoid Diversity in Chile Peppers and the Importance to Human Food Preference

Ivette Guzmán and Paul W. Bosland

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http://dx.doi.org/10.5772/intechopen.77317

Abstract

Chile peppers are valued worldwide for their distinct capsaicinoid compounds that have been used traditionally in medicine and culinary practices. With 32 known species, five of them domesticated, they provide unique chemical profiles, when consumed by humans. Capsaicinoids, the spicy compounds, are alkaloids used to deter herbivory in the wild, offering protection to the chile pepper fruit seeds. Among the 22 known capsaicinoid structures, capsaicin and dihydrocapsaicin are normally the most abundant. In humans, capsaicin binds to nociceptor TRPV1 that generates a heat sensation. Capsaicin also mitigates inflammation responses in the digestive tract and has the potential to aid in nutrient absorption. Distinct heat profiles were recently described for the five domesticated *Capsicum* species showing a difference in heat sensations specific to species and pod type. Due to the many capsaicinoid structures, we explore the implications and opportunities of having a diverse array of heat profiles in genetically diverse *Capsicum* species.

Keywords: TRPV1 receptors, pain, heat sensitization, desensitization, capsaicinoid, *Capsicum*, capsaicin, inflammation, peppers, chile peppers

1. Introduction

Chile peppers (*Capsicum* sp.) are one of the most important vegetable and spice crops in the world. *Capsicum* species are members of the Solanaceae, a large tropical family that includes tomato, potato, tobacco, and petunia. They are not related to *Piper nigrum*, the source of black pepper, nor is it related to the Guinea pepper or grains of paradise, *Aframomum melegueta*. They are one of the first crops domesticated in the Western Hemisphere about 10,000 B.C.E. [1]. In

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fact, the genus *Capsicum* was so important to humans that when they came in contact with it, five different *Capsicum* species in separate regions of the Americas were independently domesticated. One possible reason for such an early domestication is that chile peppers are well known as medicinal plants by indigenous peoples [2].

Capsicum originated in South America in an area near Bolivia and southeast Brazil. *Capsicum* then spread to North and Central America by bird dispersal. Currently, there are 32 known species with five domesticated species being *Capsicum annuum var. annuum*, *C. baccatum* var. *pendulum*, *C. chinense*, *C. frutescens*, and *C. pubescens* (**Figure 1**) [3]. There are an estimated 3000 different chile pepper types worldwide [4]. Many of these varieties are selected by cultures for their specific heat profile [5–7]. In their native habitats, *Capsicum* grows as tender perennials. In many parts of the world, however, they are grown as annuals. Being members of the Solanaceae family, they share morphology similar to that of tomatoes. However, there are significant differences between the two crops. Domesticated chile peppers have shiny glabrous simple leaves, and in general are more compact and erect than tomato. Cultivars vary from the "normal" description, so intraspecific as well as interspecific variation must be taken into account. Since domestication, many mutants have been saved by humans, for example, yellow or orange mature fruit color, unusual fruit shapes, and the mutation that causes fruit to not taste hot when consumed.

There is extensive diversity in fruit shapes, sizes and color. Among different pod types fruit length can vary from less than 1 cm to 32.5 cm., the Guinness Record for the world's largest *Capsicum* fruit [8]. Fruit growth is dependent on ovule growth, whether it is fertilized or not. The fruit is usually seeded, but seedless, parthenocarpic forms do exist. Seed number affects the fruit's growth rate rather than its growing period. When seed number increases in a fruit there

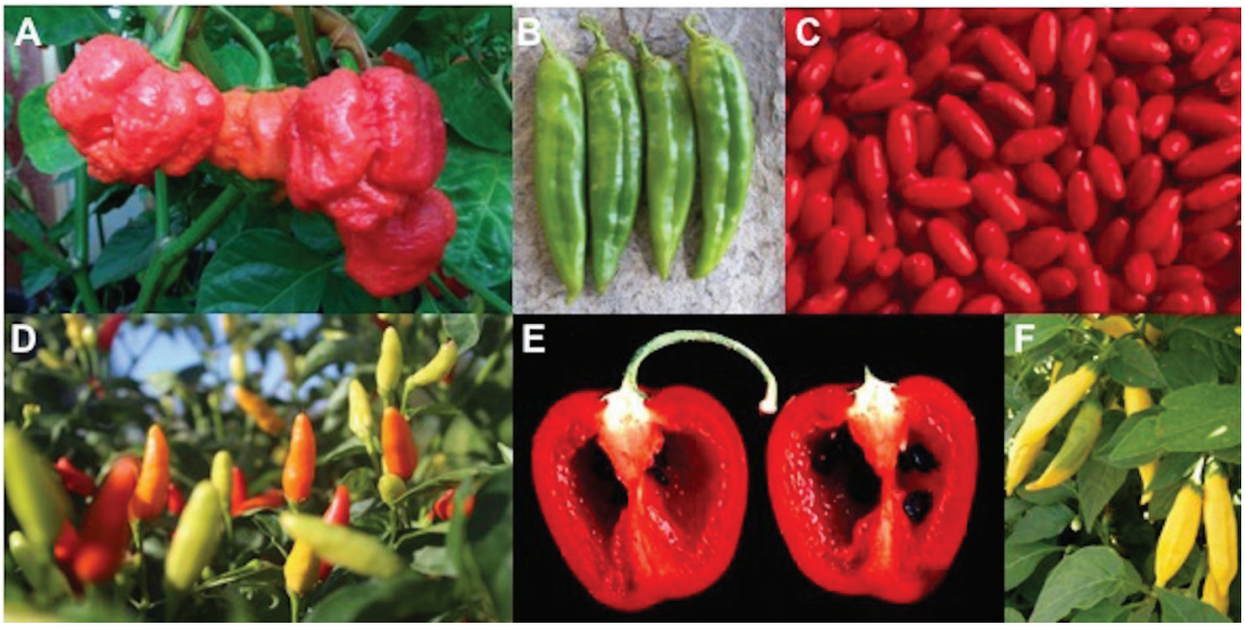


Figure 1. Selected varieties for (A) *Capsicum chinense* 'Trinidad Moruga Scorpion', (B) *Capsicum annuum* 'NuMex Heritage Big Jim', (C) *Capsicum chacoense* (wild), (D) *Capsicum frutescens* 'Tabasco', (E) *Capsicum pubescens* 'Rocoto', and (F) *Capsicum baccatum var. pendulum* 'Aji Limon'.

http://dx.doi.org/10.5772/intechopen.77317

is an inhibitory effect on fruit set and growth of later-developing fruits [8]. The pod may have two or more locules each divided by a central placenta. The placenta is the location of oleoresin and capsaicinoid production and storage vesicles. Recently, a mutation was discovered that allows the 'walls' or pericarp of the pod to produce vesicles increasing the heat level [9].

It is the capsaicinoids, alkaloids, that cause the heat sensation when consumed by mammals, that distinguishes this genus in the Solanaceae family. The primary function of capsaicinoids is to discourage mammalian feeding of the spicy chile pepper fruit, which results in destroying the seeds, while remaining attractive to birds who disperse the seeds [10]. Most Solanaceous plants have sufficiently high levels of alkaloids in their leaves that are known to be toxic to many mammals. Oddly, chile peppers do not contain alkaloids in their leaves. In fact, in the Philippines, chile pepper leaves are eaten as a leafy vegetable. Without these alkaloids, chile peppers evolved another strategy for partial protection by deterring the wrong herbivores and attracting to the desired ones, the capsaicinoids. Capsaicinoids are not toxic per se, but are ferocious enough to discourage mammalian herbivory. Birds, on the other hand, are attracted to the small red fruit on wild plants and have digestive tracts that chemically and physically soften the seed coats without damaging the seeds, thus encouraging germination. In fact, some seeds will suffer retarded germination if they do not pass through a bird's digestion system. It is suggested that capsaicinoids are the cause of slow germination of *Capsicum* seed [11]. Because birds lack the receptors in their mouth for detecting capsaicinoids, they do not taste any heat when eating very hot chile peppers. Wild chiltepins are so strongly associated with birds that a common name for them is bird pepper. Recently, it has been shown that the capsaicinoids also protect the seeds from microbial infections [12].

Capsaicinoids are used in food, and are equally important in pharmaceutical applications, as a repellent in self-defense sprays, as a rodent repellent, as an anti-inflammatory agent, as a pain reliever, and as an antimicrobial agent [2, 10, 13–21].

2. Capsaicinoid biogenesis

2.1. Capsaicinoid chemistry

Capsaicinoids consist of compounds that belong to the vanilloid group and differ in the structure of branched fatty acid (acyl) moieties attached to the benzene ring of vanillylamine [18]. The chemical structures contain three important regions; an aromatic head, an amide linkage, and a hydrophobic tail. Any variation in the chemical structure of the capsaicinoids, mainly the structure of the fatty acid chain, affects the heat profile and their pharmacological activities (**Figure 2**). Studies indicate that the aromatic head and the amide structures provide the excitation of sensory neurons while the hydrophobic tail is responsible for maximal potency [22, 23]. Currently, a total of 22 distinct capsaicinoids are found occurring naturally, each with a different hydrophobic fatty acid tail. Capsaicin (8-methyl-N-vanillyl-trans-6-nonenamide) and dihydrocapsaicin (*N*-(4-hydroxy-3-methoxybenzyl)-8-methylnonanamide) are considered the two major capsaicinoids found in chile peppers, whereas the others, e.g., nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, etc., are considered minor capsaicinoids.

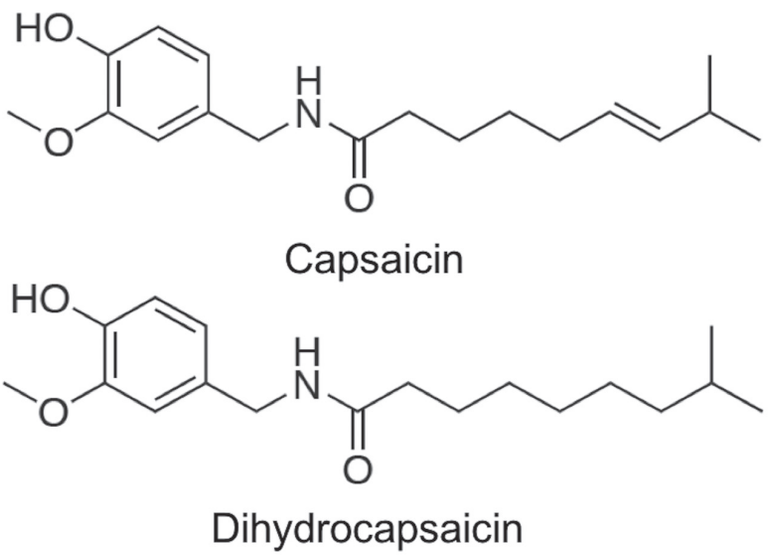


Figure 2. Chemical structures of capsaicin and dihydrocapsaicin illustrating the difference in fatty acid moiety.

Due to the slight variations in structure, each capsaicinoid creates a different heat sensation effect in the mouth [5, 24]. The variability of amount and type of capsaicinoids within *Capsicum* is enormous. For example, the wild species *C. chacoense* does not contain nordihydrocapsaicin, while other species such as *C. pubescens* can have only small amounts of capsaicin, but large amounts of the "minor" capsaicinoid, isomer of dihydrocapsaicin (**Figures 1** and **2**). The diversity of capsaicinoids has created a cultural context to eating chile peppers.

Normally in food and processing industries, the level of total capsaicinoids is converted to Scoville Heat Units (SHU), a measurement for heat level developed by Wilbur Scoville [25]. Scoville Heat Units are based on a dilution formula with the approximate number of times a standardized chile pepper extract is diluted to be imperceptible to a set of trained tasters. A modern method of calculation is to use analytical instrumentation that produces part per million (ppm) readings, followed by conversion of the ppm amounts to SHU by multiplying the ppm by 16 [26]. The hottest chile pepper cultivar, as determined by the Chile Pepper Institute is the 'Trinidad Moruga Scorpion', that has been documented to have fruits surpassing two million SHU (**Figure 1**) [27].

2.2. Capsaicinoid location in chile pepper fruits

For most *Capsicum* fruits, capsaicinoids are synthesized and accumulated in the epidermal cells of the fruit placenta within structures know as vesicles, also called "blisters." Seeds do not produce capsaicinoids but can be tainted with the capsaicinoids from the surrounding tissue containing the vesicles. Capsaicinoids are always associated with the oil producing vesicles. Even though, most chile pepper fruits are hot, there are numerous varieties that produce no heat fruit [28–30]. The *Pun1* locus, formerly known as the *C* locus, found on chromosome 2 encodes a putative acyltransferase that theoretically condenses the fatty acid (acyl) moieties to the vanillylamine benzene ring. Chile pepper varieties with heat have a functional allele, while the no heat varieties have a non-functional allele. A novel mechanism for having no heat chile pepper fruits is to lose the ability to make the vesicle structures. This locus is

http://dx.doi.org/10.5772/intechopen.77317

known as the loss-of-vesicle (lov) gene [8]. With this mutation, the plant has a functional *Pun-1* gene, but cannot express capsaicinoids because of the lack of vesicles.

The level of heat, i.e., capsaicinoid production, is genetic with a high genotype by environment interaction component. The environment can increase or decrease significantly the heat level of a given cultivar [31–36]. The capsaicinoid content can be affected by weather conditions, growing conditions and fruit age. Plant breeders selectively develop cultivars within certain ranges of heat, e.g., mild, medium, hot, superhot. Because heat level is augmented with increased environmental stress, growers can moderate heat level by the amount of stress to which they subject their plants [31, 32]. A few hot days can increase the capsaicinoid content significantly. Anthropopathically, the plant has sensed the stress, and has increased the capsaicinoid level in its fruit. If the same cultivar is grown in both a hot semi-arid region and a cool coastal region, the fruit harvested from the hot semi-arid region will be higher in capsaicinoid amounts than that the fruits harvested in the cool coastal climate. Capsaicinoids start to accumulate when fruits begin to ripen and reach their highest content when fruits reach their maximum size. Variation in capsaicinoid content has been observed in wild *Capsicum* accessions. Even *Capsicum* plants with no capsaicinoid production have been documented in the wild [12, 37].

Though Bennett and Kirby considered capsaicin and dihydrocapsaicin as the major capsaicinoids, this generalization is not true for all chile pepper varieties [38]. Collins et al. reported a capsaicinoid profile in *C. pubescens* accessions, where dihydrocapsaicin is the largest proportion, i.e., 35% dihydrocapsaicin, 29% capsaicin, 21% nordihydrocapsaicin, 8% unidentified capsaicinoid, 4% isomer of dihydrocapsaicin, 2% unidentified capsaicinoid and 1% homodihydrocapsaicin [26]. Zewdie et al. reported an unusual capsaicinoid profile in two *C. pubescens* accessions, where the isomer of dihydrocapsaicin is the largest proportion, i.e., 39% isomer of dihydrocapsaicin, 17% homodihydrocapsaicin, 13% capsaicin, 13% dihydrocapsaicin, 13% nordihydrocapsaicin, and 5% nornordihydrocapsaicin [39]. Other anomalies were found where a *C. chacoense* accession had 30% nordihydrocapsaicin, and a *C. pubescens* accession had 42% isomer of dihydrocapsaicin and 23% homodihydrocapsaicin [39].

It has been shown organoleptically that humans not only note the intensity of hotness, but perceive each capsaicinoid differently [5, 24]. The investigations of Krajewska and Powers revealed that nordihydrocapsaicin was the least irritating, and the burning was located in the front of the mouth and palate. It caused a "mellow warming effect" [24]. The heat sensation developed immediately after swallowing and receded rapidly. In comparison, capsaicin and dihydrocapsaicin were more irritating, and were described as having a "typical" heat sensation. Both compounds produced the heat in the mid-mouth and mid-palate as well as the throat and the back of the tongue. In contrast, homodihydrocapsaicin was very irritating, harsh and very shape. The heat did not develop immediately and it affected the throat, back of the tongue, and the palate for a prolonged period. After ingestion, the heat sensation can last up to 12 hours in some individuals. Different combinations of these capsaicinoids produce the chile pepper heat profile [5]. Capsaicinoids are valuable pharmacological compounds that have been studied for pain relief, weight management, cholesterol management, anti-inflammation, anti-cancer, and anti-oxidant activity.

Because of the natural variation of capsaicinoid content occurring in chile peppers, it is necessary to find their bioactivity differences in the digestive tract and afferent sensory neurons.

3. Capsaicinoid pharmacology

3.1. Capsaicinoids role in pain

Due to the prevalence of capsaicin in *Capsicum* species, most capsaicinoid pharmacological studies have focused on capsaicin. Capsaicin is used orally or as intradermal and topical applications to treat pain. Sensations of stimuli like temperature, touch, pain, taste, originate in transient receptor potential (TRP) ion channels found on afferent neurons. There are six TRP heat dependent channel families; one of which is the vanilloid type (TRPV), a group of nociceptors [40]. Capsaicin acts by binding to the TRPV1 receptor located on nociceptor neurons resulting in an influx of cytosolic calcium ions [41, 42]. This activation of TRPV1 receptors by capsaicin or temperatures above 52°C induces "hot" pain-like sensations. Other TRP receptors are sensitive to lower temperatures as well as other compounds, i.e., menthol, isothiocyanates [40, 43].

In 1968, Jancso was the first to discover that repeated doses of capsaicin induced pain initially followed by analgesia [44]. This was noticed in response to thermal, mechanical, and chemical noxious stimuli. Inhibition of the receptor function is called desensitization. Topical application of 8% capsaicin produces desensitization by decreasing pain for 12 weeks [42, 45]. Pain relieving effects of an 8% capsaicin patch lasting up to 18 months have been shown in post-traumatic patients suffering with neuropathic pain [46]. In addition, oral capsaicin has been used to treat cough because inflammation of the airways can be caused by noxious stimuli on nociceptors [47].

Even though capsaicinoids have been used for thousands of years as a medicinal compound and scientific work has proven the efficacy as a pain attenuator, the problematic issue is estimating the correct dosage for the desired response. One method to moderate response is to use different known amounts of capsaicin. For example, topical creams, lotions and patches available on the market, some even over the counter, contain different concentrations of predominantly capsaicin (0.025–0.1% wt/wt) [42]. Another method would be to use a mixture of capsaicinoids to induce a desired effect. Structural studies indicate that the aromatic benzene ring hydrogen bonds to the TRPV1 domains while the fatty acid tail uses van der Waals interactions to bind [48]. This parallels the fact that the capsaicinoid aromatic head provides the excitation of sensory neurons while the hydrophobic tail is responsible for maximal potency. Therefore, we can expect to see differences in overall effects from one capsaicinoid to another. Considering that the 22 capsaicinoids have the aromatic benzene ring in common but differ in the fatty acid tails, the possibility of each one exerting a slightly different response from the TRPV1 is possible. As mentioned previously, capsaicinoid profiles are unique in each chile pepper type and species and the unique profiles exert unique heat sensations from short lasting to long lasting [5]. Not only can different concentrations of capsaicin provide desensitization, but the other capsaicinoids could also provide varying levels pain relief.

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3.2. Capsaicinoids, inflammation and the digestive tract

There is more than one mode of action for the capsaicin induced anti-inflammation response. One is by binding to TRPV1, and the other is by regulating pro-inflammatory cytokine production pathways in neurons. By targeting capsaicin-triggered TRPV1 receptors, a select group of compounds have been shown to reduce inflammatory pain. These compounds are flavonoids like naringenin, vitexin, hesperidin methyl chalcone [42, 49]. In the stomach, binding of capsaicin to TRPV1 produces increased mucosal blood flow, mucus secretion and bicarbonate secretion [40, 50]. Employing a capsaicin blocker (capsazepine) on TRPV1, evidence confirmed that there was an increase in blood flow, hyperemia, generated by capsaicin binding to TRPV1 [50, 51]. Just like the topical applications of capsaicin, capsaicin desensitization is used with patients suffering from stomach pain associated with gastric acid, irritable bowel syndrome or irritable bladder [40, 52–54]. However, there could be a different response in the small intestine, pancreas and colon because their environments and digestive roles are different than the stomach's environment.

In the mouth, salivary gland epithelial cells (SGEC) release cytokines, such as TNFα and IL-6, both of which are associated with inflammation of salivary glands [55]. If the inflammation response is triggered too often by the cytokines, the result could lead to cancer. The same phenomena exist in the gastrointestinal tract. Striking evidence shows that capsaicin's inflammation inhibitory action in SGEC is through inhibition of the IkB-α/NF-kB signaling pathway and not TRPV1 [55]. The transcription factor NF-kB regulates the expression of cytokines TNFα and IL-6, two pro-inflammatory signals [56, 57]. Therefore, capsaicin inactivates the transcription factor associated with a pro-inflammatory response [58]. Due to the elevated risk of developing cancers from chronic inflammation, the capsaicin NF-kB interaction has been studied to suppress inflammation associated with cholangiocarcinoma, bile duct cancer, making capsaicin a potential anti-tumor compound [58, 59].

Capsaicin is also able to reduce production of inflammatory cytokines produced as a response to bacterial lipopolysaccharide (LPS) infection in human microphages [17]. After bacterial infection, LPS serves as stimuli promoting NF-kB induced pro-inflammatory cytokine production [60]. This effect is interrupted by capsaicin signaling the expressing Liver X Receptor (LXRα) that inhibits NF-kB, therefore inhibiting inflammatory cytokine production. Capsaicin's anti-inflammatory response in the gastric epithelial cells extends to inhibiting *Helicobacter pylori* bacteria cytokine production in the gut, thus reducing inflammation generated from *H. pylori* infections, a common cause of ulcers [61]. It was previously thought that spicy food caused ulcers, however, these results prove the opposite and could potentially help patients suffering from *H. pylori*-induced ulcers. The novel role of capsaicin opens up opportunities to study the influence of other capsaicinoids in the inhibition of cytokine induced inflammation.

Not only does chronic digestive tract inflammation increase the risk of cancer, but it is correlated to decreased gut nutrient absorption. A group of chronic diseases are commonly referred to as inflammatory bowel disease (IBD). Causes are sometimes unknown or could be brought on by pathogenic bacteria. All of these diseases however trigger certain factors that give rise to chronic inflammation [62]. Inflammation causes poor absorption of nutrients by altering the structure, physiology, bile amounts and microbiota of the digestive tract [63].

Patients with an IBD are deficient in minerals and vitamins like folic acid, zinc, iron, selenium, and fat-soluble vitamins like beta-carotene (pro-vitamin A) due to malabsorption [63].

Additionally, studies show that capsaicin alters the structure of the intestines promoting absorption. Small intestine segments isolated from rats who were fed with capsaicin for 8 weeks were able to absorb higher amounts of iron, zinc and calcium [64]. Veda and Srinivasan also reported an *in vivo* study where higher amounts of beta-carotene were absorbed by rats being fed beta-carotene and capsaicin [65]. With the recent work correlating capsaicin to decreased inflammatory signals and increased nutrient absorption, further work is needed to observe improved nutrient absorption with an intake of more capsaicinoids.

3.3. Capsaicinoids and absorption of chile pepper carotenoids

Due to the impact capsaicinoids, particularly capsaicin, have on nutrient absorption in the gut, other chile pepper compounds ingested simultaneously are more bioaccessible for absorption. As mentioned, beta-carotene consumed with capsaicin increased the beta-carotene amounts in rats [65]. Besides capsaicinoids, *Capsicum* species are a rich source of anthocyanins, organic acids, phenolic acids, carotenoids, tocopherols, and ascorbic acid [66]. In particular, chile peppers produce a large number of carotenoids, some of which are unique to *Capsicum* species like capsanthin and capsorubin [18]. A number of conditions and diseases (i.e., poor cardiovascular health, macular degeneration, Alzheimer's disease and dementia) may be linked to effects of malnutrition and low consumption of carotenoids like lutein and zeaxanthin [67–70]. Both lutein and zeaxanthin act as antioxidants and anti-inflammatory agents by reducing oxidative stress [71]. Macular degeneration, an age-related eye disease, is clearly associated with insufficient dietary lutein and zeaxanthin [72, 73]. Additionally, recent work found higher human serum levels of these two carotenoids in older populations showing no symptoms of Alzheimer's while lower amounts were found in a population exhibiting dementia and Alzheimer's symptoms [67, 74]. By the year 2050, there will be 106 million cases of Alzheimer's disease and dementia in the US [68]. Access to foods rich in health promoting carotenoids, such as lutein and zeaxanthin, that are bioavailable are key to prevention of age-related chronic diseases [67–70].

Chile peppers, *Capsicum* spp., are among one of the few fruits and vegetables, that produce both lutein and zeaxanthin [75, 76]. They may contain amounts up to 10.76 mg/g dry weight of total carotenoids. Two classes exist, the carotenes and the xanthophylls [18]. Carotenes include nutritionally important carotenoids like alpha-carotene and beta-carotene, all of which are provitamin A. In the mammalian stomach, carotenes are converted to vitamin A [77]. Xanthophylls such as lutein and zeaxanthin, are among the few plant compounds that are known to be absorbed by the human digestive tract [78]. They can also be passed on from the mother's diet to her breast milk and subsequently to the infant's digestive tract and blood stream [78]. Once they enter the blood stream, they reach the human retina where they make up the macular pigment [72]. Lutein and zeaxanthin are found throughout the eye tissues but are in high concentrations near the retina. Our eyes are constantly exposed to light, therefore, lutein and zeaxanthin act as a shield by filtering the sun's blue light, the most harmful wavelength responsible for creating dangerous oxidative compounds that damage our DNA, proteins and cell membranes [67, 72, 79].

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Currently, there is no recommended daily allowance (RDA) for lutein, however 6–10 mg/day have been reported to decrease macular degeneration risks [80]. Normally, a typical diet will include about 1–3 mg/day of lutein. As a result of capsaicinoids' anti-inflammation properties, beta-carotene absorption has already been shown to increase when eaten with capsaicin [65]. If a typical diet includes *Capsicum* species high in capsaicin, humans could absorb more carotenes and xanthophylls already present in chile peppers.

4. Conclusions

When reviewing capsaicinoid nutritional and medicinal properties, it is clear why over so many years, people have been saving chile pepper seeds and using them in traditional medicines and culinary practices. As we have shown, their properties go beyond adding heat and flavor to a culinary dish. Capsaicinoids have pharmacological activities that help the human body reduce pain. It also serves as an anti-inflammatory agent which not only aids in pain reduction, but also has the potential to be used to promote absorption of other essential nutrients like beta-carotene, lutein and zeaxanthin. The diversity of *Capsicum* species, each with their own diverse capsaicinoid profile, increases their versatility in pharmacology.

These approaches to reducing pain and inflammation using capsaicin and knowing that there are 21 other capsaicinoids that have yet to be characterized pharmacologically, offers new opportunities to explore *Capsicum* species diversity. Because most of the research has been done with capsaicin, and initial capsaicin treatments result in pain and burning sensations, researchers could attempt to circumvent the initial capsaicin burn by using other "not so spicy" capsaicinoids. In view of the fact that studies indicate that the capsaicinoid aromatic head provides the excitation of sensory neurons while the hydrophobic tail is responsible for maximal potency, one can expect to see differences in overall effects from one capsaicinoid to another. However, more work is needed to show the specific bioactivity of the remaining 21 capsaicinoids found in diverse *Capsicum* species and their physiological effects on cytokine pro-inflammatory mechanisms and TRPV1 induction. Each capsaicinoid could have different chemical binding properties to receptors and therefore, different *Capsicum* species could provide novel capsaicinoid formulas for specific health related treatments.

Author details

Ivette Guzmán and Paul W. Bosland*

*Address all correspondence to: pbosland@nmsu.edu

Department of Plant and Environmental Sciences, Chile Pepper Institute, College of Agricultural, Consumer, and Environmental Sciences, New Mexico State University, Las Cruces, NM, USA

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